

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K	A2	(11) International Publication Number: WO 98/27930 (43) International Publication Date: 2 July 1998 (02.07.98)
<p>(21) International Application Number: PCT/JP97/04704</p> <p>(22) International Filing Date: 19 December 1997 (19.12.97)</p> <p>(30) Priority Data: PO 4391 24 December 1996 (24.12.96) AU PO 4389 24 December 1996 (24.12.96) AU PO 5451 4 March 1997 (04.03.97) AU</p> <p>(71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): MARSTON, Hugh, M. [GB/GB]; Horseshoe Cottage, 6 Markle Steading, East Linton, East Lothian EH40 3EB (GB). KELLY, John, S. [GB/GB]; Tamarack 11, Redhall Bank Road, Edinburgh EH14 2LY (GB).</p> <p>(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).</p>		<p>(81) Designated States: CA, CN, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>
<p>(54) Title: NEW USE OF AMINOPIPERAZINE DERIVATIVES</p> <p>(57) Abstract</p> <p>This invention relates to the use of a compound of formula (I) wherein each symbol is as defined in the description, or its pharmaceutically acceptable salt, for treating and/or preventing schizophrenia, depression, stroke, and the like.</p> <div style="text-align: center;"><p>$\text{R}^1\text{-A-N} \begin{array}{c} \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \end{array} \text{N} \begin{array}{c} \text{R}^2 \\ \\ \text{N} \end{array} \text{-Y-R}^3 \quad (I)$</p></div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

DESCRIPTION

NEW USE OF AMINOPIPERAZINE DERIVATIVES

5 TECHNICAL FIELD

This invention relates to a new use of aminopiperazine derivatives and pharmaceutically acceptable salts thereof for the treatment and/or prevention of schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism in mammals.

15 BACKGROUND ART

The aminopiperazine derivatives used in this invention are known as described in PCT International Publication No. WO 91/01979 that said aminopiperazine derivatives possess the potentiation of the cholinergic activity and are useful in the treatment of disorders in the central nervous system for human beings, and more particularly in the treatment of amnesia, dementia, senile dementia and the like.

DISCLOSURE OF INVENTION

25 The present invention relates to a new use of aminopiperazine derivatives and pharmaceutically acceptable salts thereof for the treatment and/or prevention of schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism for mammals.

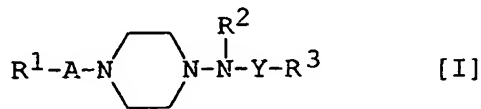
Accordingly, this invention is to provide a new use of aminopiperazine derivatives and pharmaceutically acceptable salts thereof for treating and/or preventing schizophrenia,

depression, stroke, head injury, nicotine withdrawal, spinal
cord injury, anxiety, pollakiuria, incontinence of urine,
myotonic dystrophy, attention deficit hyperactivity disorder,
excessive daytime sleepiness (narcolepsy), Parkinson's
5 disease or autism.

Further, this invention is to provide an agent and a
pharmaceutical composition for treating and/or preventing
schizophrenia, depression, stroke, head injury, nicotine
withdrawal, spinal cord injury, anxiety, pollakiuria,
10 incontinence of urine, myotonic dystrophy, attention deficit
hyperactivity disorder, excessive daytime sleepiness
(narcolepsy), Parkinson's disease or autism, which comprises
said aminopiperazine derivatives and pharmaceutically
acceptable salt thereof.

Still further, this invention is to provide a
therapeutic method for the treatment and/or prevention of
schizophrenia, depression, stroke, head injury, nicotine
withdrawal, spinal cord injury, anxiety, pollakiuria,
incontinence of urine, myotonic dystrophy, attention deficit
20 hyperactivity disorder, excessive daytime sleepiness
(narcolepsy), Parkinson's disease or autism, which comprises
administering said aminopiperazine derivatives and
pharmaceutically acceptable salts thereof to mammals.

25 The aminopiperazine derivatives used in this invention
can be represented by the following general formula [I] :



30 wherein R¹ is lower alkyl, aryl, ar(lower)alkoxy or
a heterocyclic group, each of which may be
35 substituted with halogen,

R^2 is hydrogen or lower alkyl,

R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl,

each of which may be substituted with halogen,

5 A is $\overset{\text{O}}{\parallel}\text{C}-$, $-\text{SO}_2-$ or lower alkylene, and

Y is $\overset{\text{O}}{\parallel}\text{C}-$, $-\text{SO}_2-$ or $\overset{\text{O}}{\parallel}\text{CNH}-$,

10 and pharmaceutically acceptable salts thereof.

Said compound (I) and pharmaceutically acceptable salts thereof are useful in the treatment and/or prevention of schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism in mammals.

20 Particulars of the various definitions mentioned in this specification and preferred examples thereof are explained in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, in which preferable one is methyl.

30 Suitable "aryl" may be phenyl, naphthyl, tolyl, xylyl, mesityl, cumenyl, and the like, in which preferable one is phenyl or naphthyl.

Suitable "ar(lower)alkoxy" may be benzyloxy, phenethyloxy, phenylpropoxy, benzhydryloxy, trityloxy and the like.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

5 The preferred examples of thus defined "heterocyclic group" may be an unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, 10 tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

 unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyll, benzimidazolyl, quinolyl, isoquinolyl, 15 indazolyl, benzotriazolyl, etc.;

 unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, etc.;

 saturated, 3 to 8-membered heteromonocyclic group 20 containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

 unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

25 unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl, etc.;

 unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

30 unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

 unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

35 unsaturated, condensed heterocyclic group containing 1

to 2 sulfur atom(s), for example, benzothienyl, etc.;
unsaturated, condensed heterocyclic group containing 1
to 2 oxygen atom(s), for example, benzofuranyl, etc.; or the
like.

5 Suitable "cyclo(lower)alkyl" may be cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, and the like.

 Suitable "ar(lower)alkyl" may be benzyl, phenethyl,
phenylpropyl, benzhydryl, trityl, and the like.

10 Suitable "lower alkylene" may be methylene, ethylene,
propylene, pentamethylene, hexamethylene, and the like.

 The above-mentioned "lower alkyl", "aryl",
"ar(lower)alkoxy", "heterocyclic group", "cyclo(lower)alkyl"
and "ar(lower)alkyl" may be substituted with halogen [e.g.
fluorine, chlorine, bromine and iodine].

15 Preferred compound [I] is one which has a lower alkyl,
phenyl, naphthyl or thienyl for R¹, hydrogen or lower alkyl
for R², phenyl which may be substituted with a halogen for

20 R³, $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ for A, and $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ or $\text{-SO}_2\text{-}$ for Y.

 More preferred compound [I] is one which has a lower
alkyl for R¹, hydrogen for R², phenyl which is substituted

25 with a halogen for R³, $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ for A, and $\text{-}\overset{\text{O}}{\parallel}\text{C-}$ for Y.

 Most preferred compound [I] is N-(4-acetyl-1-
piperazinyl)-4-fluorobenzamide.

30 Suitable pharmaceutically acceptable salts of the
compound [I] are conventional non-toxic salts and include
acid addition salt such as an inorganic acid addition salt
[e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.],
an organic acid addition salt [e.g. formate, acetate,
35 trifluoroacetate, maleate, tartrate, methanesulfonate,

benzenesulfonate, toluenesulfonate, etc.], a salt with an amino acid [e.g. aspartic acid salt, glutamic acid, salt, etc.] and the like.

5 It is to be noted that the compound [I] may include one or more stereoisomer(s) due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

10 Additionally, it is to be noted that any hydrate of the compound [I] is also included within the scope of this invention.

Now in order to show the utility of the compound [I] and pharmaceutically acceptable salts thereof in this invention, the pharmacological test was carried out and its abstract is
15 shown in the following.

The effect of the compound [I] upon cognitive function was examined using an operant delayed non-match to place paradigm (DNMTP) task which is shown to be disrupted dose-dependently by the administration of haloperidol. The
20 following interactions were explored: haloperidol plus amphetamine, haloperidol plus the compound [I] and haloperidol plus the compound [I] and amphetamine. Neither a low dose of amphetamine nor two doses of the compound [I]
25 when administered with haloperidol, or alone, altered the profile of performance relative to control. The experiments with haloperidol and the compound [I] plus amphetamine revealed a profound attenuation of the deficits associated with increasing doses of haloperidol by the larger dose of
30 the compound [I]. .

These experiments confirmed that the compound [I] has a specific effect on dopaminergic status which appears to be state dependent and is useful for treating ~~and/or preventing~~
35 schizophrenia, depression, stroke, head injury, nicotine

withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

5

For therapeutic purpose, the compound [I] and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral or parenteral administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

25

The following Examples is given for the purpose of illustrating this invention.

Example 1

30

(Capsule)

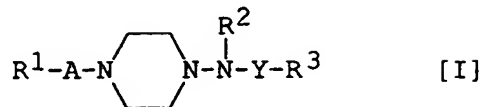
N-(4-Acetyl-1-piperazinyl)-4-fluorobenzamide	5 mg
Lactose	80 mg

The above-mentioned ingredients were mixed and the mixture was encapsulated to provide the capsule.

35

CLAIMS

1. Use of a compound of the formula :



- wherein R^1 is lower alkyl, aryl, ar(lower)alkoxy or
 a heterocyclic group, each of which may
 be substituted with halogen,
 R^2 is hydrogen or lower alkyl,
 R^3 is cyclo(lower)alkyl, aryl or ar(lower)alkyl,
 each of which may be substituted with
 halogen,

A is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-SO}_2\text{-}$ or lower alkylene, and

Y is $\text{-}\overset{\text{O}}{\parallel}\text{C-}$, $\text{-SO}_2\text{-}$ or $\text{-}\overset{\text{O}}{\parallel}\text{CNH-}$,

or its pharmaceutically acceptable salt for treating
 and/or preventing schizophrenia, depression, stroke,
 head injury, nicotine withdrawal, spinal cord injury,
 anxiety, pollakiuria, incontinence of urine, myotonic
 dystrophy, attention deficit hyperactivity disorder,
 excessive daytime sleepiness (narcolepsy), Parkinson's
 disease or autism.

2. A use of the compound defined in Claim 1 as an agent for
 treating and/or preventing schizophrenia, depression,
 stroke, head injury, nicotine withdrawal, spinal cord
 injury, anxiety, pollakiuria, incontinence of urine,
 myotonic dystrophy, attention deficit hyperactivity

disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.

3. An agent for treating and/or preventing schizophrenia,
5 depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism, which
10 comprises the compound defined in Claim 1.
4. A method for treating and/or preventing schizophrenia,
15 depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism, which
20 comprises administering the compound defined in Claim 1 to mammals.
5. A use of the compound defined in Claim 1 for
25 manufacturing a medicament for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder, excessive daytime sleepiness (narcolepsy), Parkinson's disease or autism.
- 30 6. A pharmaceutical composition for treating and/or preventing schizophrenia, depression, stroke, head injury, nicotine withdrawal, spinal cord injury, anxiety, pollakiuria, incontinence of urine, myotonic dystrophy, attention deficit hyperactivity disorder,
35 excessive daytime sleepiness (narcolepsy), Parkinson's

disease or autism, which comprises the compound defined in Claim 1 in admixture with a carrier or excipient.

- 5 7. A process for preparing the pharmaceutical composition of Claim 6, which is characterized by admixing the compound with a carrier or excipient.

10

15

20

25

30

35